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Long-term seizure outcome in frontal lobe epilepsy surgery

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ABSTRACT

Purpose: The purpose of this study was to report long-term seizure outcome in patients who underwent frontal lobe epilepsy (FLE) surgery.
Method: This retrospective study included 44 consecutive subjects who underwent resective surgery for intractable FLE at IRCCS NEUROMED (period 2001–2014), followed up for at least 2 years (mean: 8.7 years). All patients underwent noninvasive presurgical evaluation and/or invasive electroencephalography (EEG) monitoring when nonconcordant data were obtained or epileptogenic zone was hypothesized to be close to the eloquent cortex. Electroclinical, neuroimaging, surgical data, and histology were compared to seizure outcome.
Results: Mean epilepsy duration was 19 years; mean age at surgery was 31.6 years. Preoperative magnetic resonance imaging (MRI) showed a frontal lesion in 86.4 % of cases. Scalp video-electroencephalography (VEEG) monitoring detected a focal ictal onset in 90% of cases. Twenty-seven patients (61.4%) underwent invasive recordings. Resections involved dorsolateral (47.7%), medial (9%), orbital (13.6%), and rolandic (13.6%) region. Lobectomy within functional boundaries was performed in the remaining 7 cases (16%). Transient and permanent neurological deficits were observed in 2 and 3 cases, respectively. Histology revealed focal cortical dysplasia (45.5%), World Health Organization (WHO) I–II grade tumors (15.9%), gliosis (22.7%), vascular malformations (4.5%), Rasmussen encephalitis (6.8%), and normal tissue (4.5%). At last observation 68.1% of patients were in Engel's class I, 11.4% in class II, 9% in class III, and 11.4% in class IV. A favorable outcome was associated with focal ictal scalp EEG onset ($p = 0.0357$).
Conclusion: Surgery is a safe treatment option in drug-resistant FLE with a satisfying long-term outcome. These data highlight the importance of an appropriate selection of potential surgical candidates.
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1. Introduction

The frontal lobe is commonly involved in surgical procedures for focal epilepsy [1,2]. The rates of seizure freedom after frontal lobe resections range in the different series from 20 to 60%, lower than those reported in mesial temporal lobe epilepsy (TLE) syndrome [3,4]. The reasons for the less favorable seizure outcome after frontal lobe epilepsy (FLE) surgery are still debated in the current literature [5–7]. In particular, both anatomical and pathophysiological aspects were hypothesized to play a crucial role in determining a worse postoperative outcome. In fact, as opposed to the well-defined anatomical and ultrastructural boundaries of the mesial temporal lobe, the cytoarchitectural heterogeneity of the larger frontal lobe together with its multiple connections may result in different pathways of seizure spread with possible multilobar involvement [8]. Furthermore, the potential morbidity related to frontal corticosubcortical critical structures (i.e., primary motor cortex and pyramidal tract, supplementary motor area, Broca's area, language pathways) may limit the surgical resection even of clear and circumscribed epileptogenic lesions [5,7]. Several studies have attempted to identify some predictors of sustained seizure freedom after frontal lobe resections. Although, it is often difficult to compare surgical series because of their heterogeneity in terms of preoperative study (invasive vs. noninvasive recordings, intra- vs. extraoperative electrocorticography [ECoG], subdural vs. depth electrodes), type of resection, and length of the follow-up period; however, different factors, including focal lesion visible on magnetic resonance imaging (MRI), focal ictal electroencephalography (EEG), surgery in nondominant hemisphere, and early intervention, were found to positively affect long-term seizure outcome [1,3,6,9–16].

In the present study, we retrospectively analyzed a series of 44 consecutive patients who underwent frontal lobe resections for drug-resistant focal epilepsy. Demographic characteristics, electroclinical,

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and MRI findings as well as surgical aspects and histopathological data were collected and compared to seizure outcome and then discussed with the current literature.

2. Methods

2.1. Patients population and preoperative evaluation

This study is a retrospective analysis of consecutive adult patients who underwent respective epilepsy surgery at Neuromed Institute (Pozzilli, IS) between June 2001 and September 2014. All patients met the following inclusion criteria: drug-resistant focal epilepsy [17], frontal lobe seizure onset, available postoperative follow-up of at least two years. Preoperative evaluation included prolonged video-EEG (VEEG) monitoring [18], 1.5–3 Tesla MRI (General Electric [GE] MEDICAL SYSTEMS SignaHDxt), and neurological and neuropsychological examinations. In selected cases, interictal FDG-PET, spectroscopy, and functional MRI were also performed. All the patients of this series had given their informed consent to any invasive procedure and to the processing of both medical and biological data.

2.2. Invasive recordings

Long-term invasive VEEG monitoring was performed in those cases in which noninvasive data showed nonconcordant anatomo-electro-clinical findings, when MRI study did not reveal any clear epileptogenic lesion, or the epileptogenic zone (EZ) was hypothesizedLong-terminvasive VEEG monitoring was performed in those cases in 99 which noninvasive data showed nonconcordant anatomoelectroclinical 1Q008 findings; MRI study did not reveal any clear epileptogenic lesion, or the epileptogenic zone (EZ) was hypothesized.

Invasive recordings were mainly obtained through subdural grid and/or strip electrodes implantation. In one patient, three contralateral depth electrodes were additionally implanted through a stereotactic procedure since an early contralateral seizure spread was suspected. The surgical procedure for subdural electrodes positioning has been described elsewhere [19] and required in all cases a craniotomy under general anesthesia. In each patient, the implantation strategy (i.e., number of electrodes and contacts, size and position of craniotomy, extent of cortical coverage) was tailored on the localizing hypothesis derived from noninvasive investigations. Given the amount of contacts implanted per patient (64 contacts on average, range 48–86), the dural flap closure was completed by a small duraplasty (Fig. 1) to enlarge the subdural space and to prevent potential side effects of the electrode-induced brain swelling (i.e., atypical seizures, brain shift, intracranial hypertension). Postoperative corticosteroids and mannitol solutions were routinely administrated for the same purpose. Standard intra- and short-term perioperative antibiotic prophylaxis was performed by the use of first generation cephalosporins. The single contacts location was detected both through surgical snaps of the exposed cortex and by means of a semiautomated MATLAB routine for processing of postimplantation volumetric (slice thickness 0.625, gap 0) computed tomography (CT) scans [20] (Fig. 2).

Invasive video-ECoG recordings were obtained in patient's rooms and lasted on average 55.2 h (range 36–336 h). In selected cases, the antiepileptic drugs were reduced according to seizure frequency. Bipolar and monopolar recordings of basal rhythms and interictal and ictal activity were analyzed in all cases by the use of a 128-channel Grass-Telefactor system with a sampling rate of 256 Hz.

In patients with epileptogenic zone close to motor and/or Broca's areas, the invasive study was completed by cortical stimulation for functional mapping. Bipolar stimulations (50 Hz, 0.3- msec single pulse duration, 16-msec interstimulus interval [ISI], 1- to 7-sec train duration) were delivered through selected subdural contacts at various intensities (ranging from 0.2 to 0.5 mA for motor cortex and from 5 to 15 mA for speech areas) during video-ECoG monitoring and neuropsychological testing. A dose of 15 mg/kg phenytoin was administrated as a 45-minute infusion to avoid potential afterdischarges and stimulation-related seizures. The mean duration of cortical mapping was 3.5 h (range 2–7).

2.3. Surgical procedures

Surgery after noninvasive investigations was performed in patients with proved lesion-related epilepsy and strictly consisted in lesion removal. Resective procedures after invasive study included both epileptogenic lesions removal and “tailored” cortectomies (removal of nonlesional tissue tailored on the ECoG recordings). Each procedure was performed under general anesthesia. When required a continuous monitoring of the motor pathways was obtained under total intravenous anesthesia (TIVA) with target-controlled infusion (TCI) of remiphentanil and propofol. All the resective procedures were conducted through high magnification microsurgical technique (OPMI Pentero 10×) (Fig. 3).

2.4. Follow-up

All patients underwent brain neuroimaging study (CT or MRI) within first week after surgery. Scheduled follow-up MRI, EEG, neurological, and neuropsychological evaluations were performed at 1, 2,

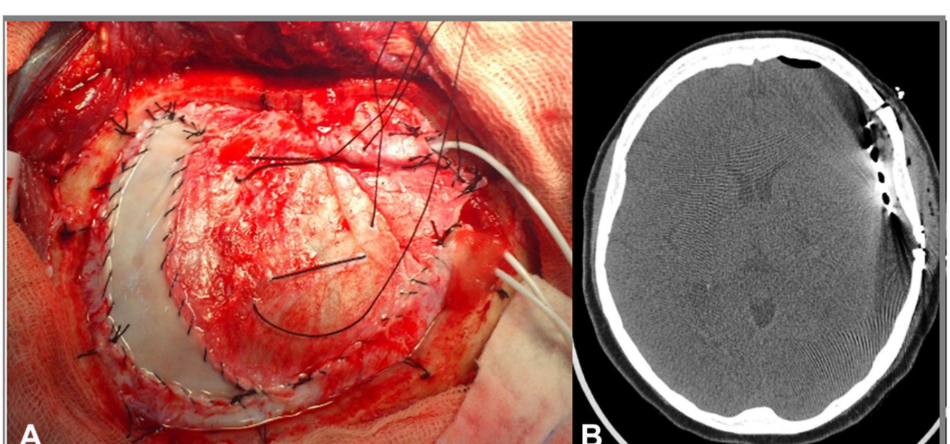

Fig. 1. Dural flap closure with small duraplasty over a large subdural grid (A). Postimplantation Axial CT scan with no evidence of brain shift (B).

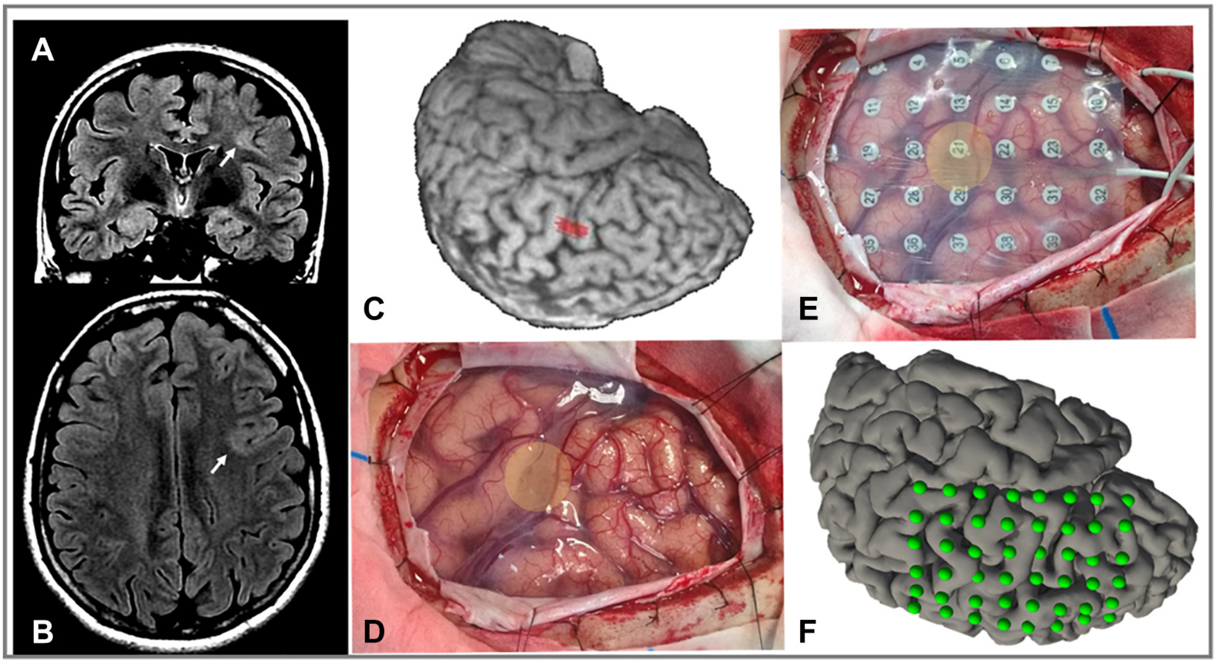

Fig. 2. Subdural contacts reconstruction both through the digital photography of the exposed cortex (D–E) and the MATLAB routine (F). The lesion, a type II FCD (A–B), is also reconstructed in 3D MRI and projected on the surgical field (C-D-E).

and 5 years after surgery in all subjects. With regard to patients with histological evidence of tumors, further neuroradiological studies were performed. Seizure outcome was yearly defined according to Engel's classification by the patient's report to the neurologist during follow-up visits [21].

2.5. Statistical analysis

A descriptive analysis was used to study the frequency distribution of all variables of interest. Subsequently, the Fisher's exact test was used as appropriate to analyze differences in categorical variables between participants with best definitive seizure outcome (Engel's class Ia, seizure-/aura-free) and those with persistence of aura and/or seizures (Engel's class Ib-IV), while the *t*-test was used to analyze differences in continuous variables. The level of significance was fixed at $p < 0.05$.

3. Results

A total of 44 consecutive adult patients (25 male) were included in the retrospective study. Their mean age at surgery was 31.66 years (range 4–59 years, SD $\pm$ 13.33); mean epilepsy duration was 19.12 years (range 1–51 years, SD $\pm$ 13.22). Neurological examination was remarkable for focal signs in 8 cases and mild cognitive disabilities in 5 cases. In 38 (86.4%) out of 44 patients, preoperative MRI showed a lesion located in frontal lobe structures. Seizures were classified as focal-impaired awareness in 22 patients (50%), focal to bilateral tonic–clonic in 20 cases (45.5%), and focal aware in the remaining two cases (4.5%). Seizure frequency was reported to be monthly in 13 (29.6%), weekly in 19 (43.2%), daily in 10 (22.7%) patients.

Seizure semiology was variable: focal clonic in 7 patients (16%), tonic-postural in 15 (34%), hyperkinetic in 20 (45%), and nonmotor with behavioral arrest in 2 (5%). Tonic-postural and hyperkinetic

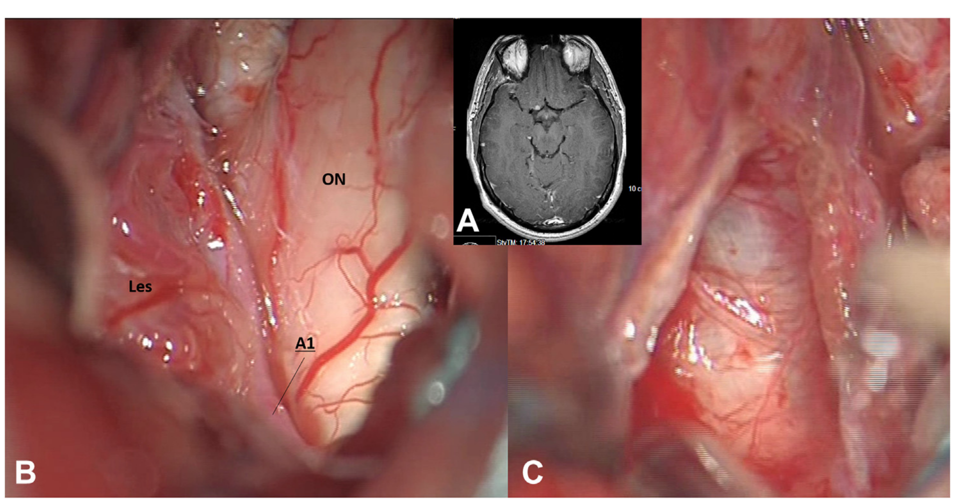

Fig. 3. High magnification microscopic view of a small frontal basal ganglioglioma (A–B). After lesion removal the optic chiasm is visible through the pial surface (C). ***Abbr.*** **Les:** lesion; **A1**: A1 tract of the anterior cerebral artery, **ON:** optic nerve.

Table 1
Resective procedures in the population.

N° of patients (%)	MRI findings	Invasive recordings	Surgical procedures
28 (63%)	Positive	11	Lesion removal
10 (23%)	Positive	10	Lesion removal + cortectomy
6 (14%)	Normal	6	Tailored cortectomy
Total 44		27	

seizures were recorded in 4/6 (67%) patients without lesion and in 29/38 (76%) patients with positive MRI results.

Scalp VEEG monitoring allowed to record focal ictal onset in 40/44 cases (90%). In 17 out of 38 patients (44.7%) with radiological evidence of a focal lesion, the concordance of presurgical noninvasive investigations, allowed us to offer a lesionectomy (Table 1). The remaining 27 (61.4%) out of 44 patients (21 with lesional and 6 with epilepsy of unknown cause) underwent invasive VEEG recordings before resective surgery. Cortical stimulations for functional mapping were performed in a total of 8 cases (29.6%): in 3 of them the epileptogenic zone was found to be partially overlapped with the functional cortex. No overlap was detected in the remaining 5 cases.

After invasive investigations, resective procedures included lesionectomy in 11/27 cases (40.7%), lesionectomy plus tailored cortectomy in 10/27 cases (37.1%), and tailored cortectomy in the remaining 6 cases with epilepsy of unknown cause (22.2%) (Table 1).

Overall resective procedures involved the dorsolateral frontal structures in 21 patients (47.7%), the medial frontal region in 4 cases (9%), the polo-orbital region in 6 cases (13.6%), and the rolandic area in 6 cases (13.6%). The remaining 7 patients (16%) underwent extensive frontal lobe resections within functional boundaries. The left hemisphere was involved in 21 patients (47.7%).

Among the 38 patients with symptomatic epilepsy, postoperative MRI showed total lesion removal in 35 cases (92.1%). As expected, a subtotal removal was confirmed in all the 3 cases in which the functional mapping had detected a partial overlap between lesion and the eloquent cortex.

Transient neurological deficits were observed in 2 cases (4.5%), consisting of hemiparesis and dysphasia respectively, while 3 other patients experienced permanent motor deficits (6.8%).

Histopathological examination revealed low grade tumors (World Health Organization [WHO] grade I–II) in 7 patients (15.9%), focal cortical dysplasia (FCD) in 20 cases (45.5%) (type I in 8 cases, type II in 12 cases [22,23]), gliosis in 10 cases (22.7%), vascular malformations in 2 cases (4.5%), inflammatory disease in 3 cases (6.8%), and normal tissue in the remaining 2 cases (4.5%).

The mean postoperative follow-up period was of 8.7 years (range 2–15, SD ± 3.49). With regard to seizure outcome, at the last follow-up examination, 30 patients (68.1%) were classified in Engel's class I (24–54.5% in Engel's class Ia, 2–4.5% in class Ib, 1–2.3% in class Ic, and 3–6.8% in class Id), 5 patients (11.4%) in Engel's class II, 4 (9.0%) in Engel's class III, and the remaining 5 (11.4%) in class IV. At univariate analysis the association between seizure outcome and focal ictal scalp EEG was statistically significant ($p = 0.0357$) (Table 2).

4. Discussion

In the present study, we reported a series of 44 consecutive patients who underwent frontal lobe resections for drug-resistant focal epilepsy. Long-term seizure outcome was found substantially favorable and significantly associated with focal ictal scalp EEG.

Seizure outcome after FLE surgery has been investigated by various studies attempting to identify possible predictors of treatment response, with conflicting results. In their systematic review, Englot DJ and colleagues [13] examined 21 studies, accounting a total of 1119 patients surgically treated for refractory FLE. The overall rate of patients in

Table 2
Pre- and postsurgical variables in patients with Engel's class Ia vs. patients with Engel's class Ib-IV: univariate analysis.

Dependent variable		Patients with favorable outcome (Engel Ia) N° (%)	Patients with unfavorable outcome (Engel Ib-IV) N° (%)
Age at epilepsy onset (mean ± SD)		13.88 ± 8.65	10.10 ± 11.35
Epilepsy duration (mean ± SD)		21.21 ± 15.46	15.65 ± 9.90
Seizure frequency	Rare (<12/year)	2 (4.5)	2 (4.5)
	Monthly	7 (16)	5 (11.4)
	Weekly	10 (22.7)	8 (18.1)
	Daily	5 (11.4)	5 (11.4)
Preoperative MRI	Positive	22 (50)	16 (36.4)
	Normal	2 (4.5)	4 (9.1)
Seizure type	Hyperkinetic	13 (29.5)	7 (16)
	Clonic	3 (6.8)	4 (9)
	Tonic-postural	7 (16)	8 (18.1)
	Hypomotor	1 (2.3)	1 (2.3)
Ictal scalp EEG	Focal	24 (54.6)*	16 (36.4)
	Multifocal	–	2 (4.5)
	Diffuse	–	2 (4.5)
Invasive recordings	Yes	15 (34.1)	12 (27.4)
	Not	9 (20.4)	8 (18.1)
Surgery (side)	Dominant	10 (22.7)	11 (25.1)
	Nondominant	14 (31.8)	9 (20.4)
Surgery (type)	Lesionectomy	15 (34.1)	13(29.5)
	Lesionectomy + Cortectomy	7 (16)	3 (6.8)
	Cortectomy	2 (4.5)	4 (9.1)
Surgery (topography)	Dorsolateral	14 (31.8)	7 (16)
	Medial	2 (4.5)	2 (4.5)
	Polo-Orbital	4 (9.1)	2 (4.5)
	Rolandic	2 (4.5)	4 (9.1)
	Lobectomy	2 (4.5)	5 (11.4)
Lesion removal	Total	19 (50)	16 (42.1)
	Subtotal	–	3 (7.9)
Histological examination	Low-Grade Tumors	4 (9.1)	3 (6.8)
	FCD Type I	2 (4.5)	6 (13.6)
	FCD Type II	9 (20.4)	3 (6.8)
	Gliosis	5 (11.4)	5 (11.4)
	Vascular Malformation	1 (2.3)	1 (2.3)
	Inflammatory	2 (4.5)	1 (2.3)
	Normal	1 (2.3)	1 (2.3)

* $p < 0.05$.

Engel class I after surgery was 45.1%. Seizure outcome was found to be independent by factors such as patient's age and sex, seizure type, localized ictal EEG, type of recordings (scalp compared with invasive EEG monitoring and/or intraoperative ECoG) as well as side of resection. The main predictors of favorable seizure outcome resulted to abnormal MRI, particularly focal, discrete lesions such as tumors and cortical dysplasia (52.2–54.4% seizure freedom), defined frontal lobe resections (34.3–54.8%), and gross total lesion removal (60.8%). Interestingly, the authors did not observe any trend in seizure freedom rates during the reference period (from 1990 to 2010) despite potential advances in neuroimaging, electrophysiological, and surgical techniques. Holtkamp M et al. [14] reported a series of 25 patients who underwent frontal lobe resection for intractable epilepsy after intracranial recordings, with a rate of seizure freedom of 60%. Only 6 patients had focal epileptogenic lesions and only half of them became seizure-free after surgery. In this series, the worst seizure outcome was correlated with a rapid seizure spread observed thanks to intracranial recordings and with surgery in the dominant hemisphere.

In another retrospective study of 58 patients with FLE, Lazow et al. [15] reported an overall seizure freedom rate of 57% after surgery. The average follow-up period was of >6 years. About the 93% of the patients of this series had undergone intracranial EEG monitoring. Contrary to prior studies, the authors did not find any predictive value of positive MRI, type of lesion, sublobar extension of the EZ, ictal onset EEG pattern and side of surgery. In addition, long-term results showed in 41% of cases a "relapsing–remitting" course with a trend to switch from an outcome class to another over time. Recently Ramantani and colleagues [24] reported a series of 75 consecutive children and adolescents operated on for FLE and followed up for over a year (mean 8.1, range 1–14.5 yrs) with a seizure freedom rate of 63%. They found a significant correlation between the rate of seizure freedom and short epilepsy duration (p-value 0.02). Others predictors of good seizure outcome resulted to regional interictal EEG (p-value 0.09) and epileptogenic lesion and/or zone far from eloquent cortex (p-value 0.012). Conversely, early postoperative seizures, residual lesion on MRI and epileptic discharge on postoperative EEG were significantly associated with high rate of seizure recurrence (p-value <0.001 and 0.02). Interestingly, despite this series mainly included symptomatic cases (MRI positive in 93% of patients) with high rate of FCD (71%), no significant correlation was found between seizure outcome and lesion type. Bonini et al. [25] investigated the long-term outcome (up to 10 yrs) of 42 patients with FLE who underwent resective surgery mostly after stereo-EEG (SEEG). The authors reported a seizure freedom rate of 57.1% at the last follow-up visit. Predictors of favorable outcome in their series were complete EZ resection as per SEEG findings, FCD at histological examination combined with complete resection, and focal EEG in patients with FCD. No significant difference was found in postsurgical outcome between patients with negative MRI and those with evidence of lesion. Since most of the patients included in our study showed a clear lesion on MRI, it might be interesting to compare their seizure semiology with that occurring in the well-known Nocturnal FLE (NFLE), recently renamed Sleep-Related Hypermotor Epilepsy (SHE), where MRI usually fail to disclose any abnormal findings [26]. The clinical spectrum of SHE comprises distinct paroxysmal sleep-related attacks of variable duration and complexity ranging from very brief motor attacks to hypermotor seizures. The most common feature of hypermotor seizures is hyperkinetic with bimanual and bipedal automatisms, sometimes ballistic and violent movements associated with explosive vocalization like screaming or laughing. Awareness is frequently preserved but the patient is unable to control the motor behavior. By reviewing ictal semiology in the present FLE series, we did not observe any significant difference in ictal semiology between MRI negative and positive cases, but the small sample size prevented us to draw firm conclusion on this specific issue.

In the present series, the rate of seizure freedom (Engel's class I) was relatively high (68.1% with 54.5% Engel's Ia) compared to previous reports. In line with Englot et al. [13], the postoperative outcome was independent from type of EEG recordings (scalp compared to intracranial) and was favorably influenced by abnormal preoperative MRI (57.8% Engel's I), defined frontal resections (66.6% Engel's I in dorsolateral resections) and gross total lesion removal (65% Engel's I). In our experience, the routine use of high magnification microsurgical technique was helpful for dissecting pathological from normal tissue to achieve gross total lesion removal (92.1% of cases of this series). Among lesions, FCD type II was found to be associated with favorable outcome since 9/12 (75%) patients with such histological finding were seizure-free after surgery [13,22,23,25].

According to previous reports [14], surgery in the dominant hemisphere was associated with a less favorable outcome despite the use of intracranial electrodes for cortical mapping of language areas. In line with the recent report of Ramantani et al. [24], focal EEG was in the present series the main significant prognostic factor associated with favorable outcome ($p = 0.0357$), We also found high seizure freedom rate in patients with hypermotor seizures (65% of patients in Engel's class I), confirming that hyperkinetic behavior may be a typical manifestation of epileptic activity arising from the frontal lobe [26–28].

In spite of some interesting findings, this study appears to be limited by several factors including its retrospective nature, the small sample size and the heterogeneity of the enrolled cohort in terms of etiology of epilepsy and type of surgery. Moreover, neither neuropsychological nor psychiatric profiles have been considered in the present analysis, thus preventing us to determine their potential prognostic significance. However, cognitive and psychiatric aspects in patients with FLE have been rarely evaluated as predictors of seizure outcome and their value is still controversial [15]. Finally, all patients came from a single site, and the findings may not generalize with other epilepsy centers. Considering these limitations, our results cannot allow us to draw any definitive conclusions and prevent us to clearly identify prognostic factors that could properly guide patient's selection for resective frontal lobe surgery.

5. Conclusions

Surgery can be a safe therapeutic option in drug-resistant FLE with a satisfying long-term outcome. Although our findings are in agreement with the current literature on FLE surgery, the discrepancies among the different series prevent us to identify unambiguous prognostic factor that could properly guide patient's selection for resective frontal lobe surgery. Further studies with larger and homogeneous samples are needed in order to define the real risk/benefit ratio and to identify among the population with FLE which patients could better respond to surgery.

Declarations of interest

None.

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